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LEADING ARTICLE

Lithium in the Treatment of Major Depressive Disorder

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Abstract Recent high-quality studies have confirmed the central role of lithium in the treatment of bipolar disorder and have established lithium as the drug of first choice for long-term prophylaxis in this condition. However, several indications for its use in unipolar major depression are also based on sound evidence. This includes lithium augmentation as a main strategy for depressed patients not responding to an antidepressant, lithium prophylaxis for recurrent unipolar depression as an alternative to prophylaxis with an antidepressant, and lithium's unique antisuicidal properties. Lithium monotherapy, on the other hand, is not established for acute treatment of depression. Lithium therapy should be a core competency of every psychiatrist, enabling the safe use of lithium, to the benefit of our patients.

Key Points

In unipolar major depression, lithium augmentation is a key strategy to treat patients who have not responded to an antidepressant.

While lithium is the drug of first choice for long-term prophylaxis in bipolar disorder, lithium prophylaxis for recurrent unipolar depression is a second-line alternative to antidepressants.

Lithium is the only drug with an established antisuicidal efficacy in affective disorders.

1 Affective Disorders

Lithium is mainly used for acute and prophylactic treatment of affective disorders. Affective disorders are highly prevalent and disabling conditions. Prototypically, they present as manic or as depressive episodes. A single depressive episode (also known as a major depressive episode) is diagnostically differentiated from a recurrent depressive disorder (also known as unipolar recurrent depression) and from bipolar disorder (or manic-depressive illness) with both manic and depressive episodes (Fig. 1). Single manic episodes and unipolar recurrent mania are very rare. Mixed types also exist. The main treatment goals in affective disorders are the acute treatment of a manic or a depressive episode and long-term prophylactic treatment to prevent new manic or depressive episodes. This article focuses on acute and prophylactic treatment with lithium in major depression (single depressive episode and unipolar recurrent depression).

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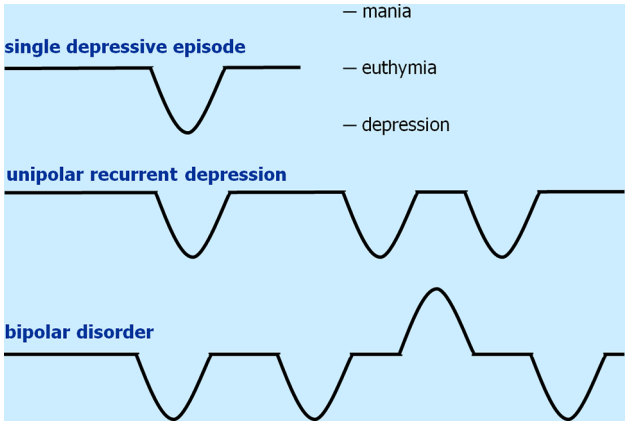

Fig. 1 Course of affective disorders

2 History of Lithium

Lithium is an old substance. When the first galaxies came into being around 14 billion years ago, the world consisted of only hydrogen, helium, and traces of lithium. The pharmacological use of lithium started in the nineteenth century, when the Danish psychiatrist and neurologist Carl Lange reported a prophylactic effect of lithium carbonate on recurrent depression [1]. Modern lithium treatment started in 1949 with the discovery of lithium's anti-manic properties by the Australian John Cade [2]. In view of the recurrent course of bipolar illness, it was no surprise that nearly 15 years later the prophylactic effect of long-term lithium therapy was evaluated and established by two Danish researchers: Schou and Baastrup [3, 4]. Shortly after lithium treatment was recommended for acute and prophylactic treatment of bipolar illness, Baastrup et al. [5] reported on the prophylactic efficacy of lithium for recurrent (unipolar) depression (see below).

With regard to bipolar illness, lithium is today the treatment of first choice for long-term prophylaxis of new episodes [6–9]. It is the only substance with a proven ability to prevent both new depressive and new manic episodes in studies without enriched design (a design that favors the investigator's drug over the comparator) [7]. It is one pharmacological option beside several others for the acute treatment of mania [10]. However, indications for use in major (unipolar) depressive disorder are also clear-cut.

3 Lithium for Prophylactic Treatment of Major Depressive Disorder

Due to high methodological requirements, a Cochrane meta-analysis included only three placebo-controlled trials of lithium for prophylactic treatment of recurrent major depressive disorder. This analysis showed that lithium was significantly more effective than placebo in preventing new depressive episodes (odds ratio [OR] 0.46, 95 % confidence interval [CI] 0.26–0.80, $p = 0.007$) [11]. Although bipolar disorder was an exclusion criterion, some study participants developed a first manic episode. With regard to depressive and manic recurrences combined, lithium scarcely failed to show a significant benefit (OR 0.14, 95 % CI 0.02–1.27, $p = 0.08$). A more recent Cochrane review of the same group compared lithium with antidepressants (eight studies were included) and found significant evidence for prophylactic efficacy of both lithium and antidepressants in unipolar depressive disorder [12]. With regard to efficacy and tolerability outcome parameters, no significant differences between lithium and antidepressants were found. The only exception was that lithium was significantly superior to antidepressants in preventing relapses that required admission to hospital [12]. Long-term studies confirm the effectiveness of lithium prophylaxis for recurrent major depressive disorder in everyday clinical practice (e.g., [13]).

Nevertheless, most guidelines on major depression prefer long-term treatment with antidepressants over lithium for the prevention of new depressive episodes [14–16]. This is mainly because lithium treatment is regarded as more complex and risky (see below). On the other hand, nearly all antidepressants share a similar mode of action, i.e., the increase of monoamines (mainly serotonin and norepinephrine) in the synaptic cleft of the central nervous system. Hence, in prophylactic non-responders to an antidepressant, it is not recommended to try one antidepressant after another, and to ignore lithium with its completely different and unique mode of action (i.e., intracellular). In addition, some guidelines clearly recommend lithium as first choice for prophylactic treatment of unipolar depression for patients at risk of suicide (see below) [14].

4 Lithium for Acute Treatment of Major Depressive Disorder

Besides prophylactic use, the efficacy of lithium monotherapy for the treatment of an acute depressive episode was tested in the 1970s and 1980s. A review found seven randomized double-blind studies [17]. Lithium was as effective as or even superior to tricyclic antidepressants (TCAs), and outperformed placebo in the two placebo-controlled trials [18, 19]. However, these older studies are small in case size (maximum of 45 patients) and have several methodological shortcomings, e.g., mixed samples of unipolar and bipolar depression. The only comparison of lithium monotherapy with a modern antidepressant for the treatment of acute unipolar depression found lithium to be inferior to citalopram [20]. As a result, lithium

monotherapy is not an established treatment for acute major depression. It should only be considered for non-responders to more established treatment options. Lithium monotherapy has been regarded as a safe and effective treatment of bipolar depression for a long time; however, recent systematic re-evaluations have concluded that its efficacy for this indication is not well proven [6, 9, 21]. Nevertheless, lithium has a well established place in the treatment of acute major depressive episodes in the form of lithium augmentation.

5 Lithium Augmentation

Lithium augmentation is a strategy of treating depressed patients who have not responded to an antidepressant [22] and was first described in 1981 [23]. Lithium augmentation involves the addition of lithium to an antidepressant that after a sufficient period of time has proven not to be effective [24]. Ten double-blind, randomized trials compared lithium augmentation with placebo augmentation in antidepressant non-responders. Lithium augmentation was significantly more effective, with an OR of 3.1 (95 % CI 1.8–5.4) and a number needed to treat (NNT) of five [25, 26]. In these studies, it was mainly TCAs that were augmented with lithium. Only two studies investigated the augmentation of selective serotonin reuptake inhibitors (SSRIs) [27, 28]. After the required pre-treatment checkups (see below), the lithium dose can be increased rather quickly. A cumulative meta-analysis revealed that presumably usual therapeutic serum concentrations in the range of 0.6–0.9 mmol/L are needed for effective augmentation. After reaching this range, the patient's response should be observed for 2 weeks [29]. If no response is seen after this time, lithium should be discontinued.

As the result of a double-blind, placebo-controlled study, it is recommended to continue the combination of lithium and the antidepressant in lithium augmentation-responders for 6–12 months. In this only study on lithium augmentation in the continuation phase of the treatment, 29 responders to lithium augmentation were randomly assigned to continued lithium or placebo for another 4 months, while the antidepressant was maintained in both groups. Nearly one-half of the patients in the placebo plus antidepressant group relapsed, while no patient relapsed in the lithium plus antidepressant group ($p = 0.006$). Only after lithium was also tapered in the active comparator group did more than one-third of these patients also relapse [30, 31]. On the other hand, if the patient does not respond after 2 weeks within the therapeutic serum level range, the lithium treatment should be stopped, except if there is a second indication for lithium.

Because of its well proven efficacy and as a strategy especially developed for the frequent clinical challenge of a patient unresponsive to an antidepressant alone, lithium augmentation is recommended by current clinical guidelines [14, 15, 32]. Antidepressants share a similar mode of action; therefore, it might be advisable in these cases to introduce new pharmacological principles [33]. Treatment strategies for these non-responders that involve antidepressants only, such as increasing the dose of SSRIs [34] or switching to another antidepressant [35], proved to be no more effective than simply continuing with the ineffective dose or drug.

Lithium augmentation is especially preferred in patients who tolerated the previous antidepressant well and should not be withdrawn from it, in patients with an indication for a prophylactic lithium treatment because of a recurrent course of illness, in bipolar depression where lithium is an option for preventing a switch into mania, or in patients experiencing suicidality (see below).

6 Suicide Prevention

One-half to two-thirds of suicide victims suffer from depression [36]. Lithium is the only drug with an established anti-suicidal efficacy for affective disorders. Tondo et al. [37], in a meta-analysis of 22 studies (over 33,000 patient-years of risk), showed that suicides were 82 % less frequent during lithium treatment than during non-lithium treatment. The same group confirmed this result in a pooled analysis of 34 studies (over 64,000 patient-years of risk) and demonstrated that lithium treatment leads to a normalization of suicide and suicide attempt rates in patients with affective disorders [38]: the rates under lithium were comparable to those in the general population. Subgroup analysis revealed that lithium is especially effective in reducing suicides and suicide attempts in unipolar depression [38].

This was confirmed by another meta-analysis, which was restricted to unipolar major depressive disorder (pooled relative risk [RR] 4.24, 95 % CI 1.49–12.0, $p = 0.007$) [39]. The most recent review by Cipriani et al. [40] is restricted to randomized controlled trials (vs. placebo or vs. an active comparator). It again found a significantly lower suicide rate in favor of lithium (OR 0.13, 95 % CI 0.03–0.66). Results were the same when restricted to unipolar depression (OR 0.13, 95 % CI 0.02–0.76). Additionally, the authors found a significantly reduced overall mortality under lithium compared with placebo or active comparators (OR 0.38, 95 % CI 0.15–0.95), which most likely is a result of reduced cardiovascular mortality, in addition to the anti-suicidal effects [8].

The only prospective, randomized, placebo-controlled trail ever published with the primary outcome of preventing suicides and suicide attempts compared 52 weeks of double-blind lithium treatment ($N = 84$) with placebo ($N = 83$) in participants with an affective disorder and a high suicide risk [41]. All subjects received treatment as usual, in addition to lithium or placebo. The primary outcome (number of suicides and suicide attempts combined) did not differ significantly (seven receiving lithium vs. ten receiving placebo), but the number of completed suicides was significantly lower in the lithium group (zero vs. three; $p = 0.049$).

Anti-suicidal properties could not be found for other psychotropic drugs used to treat affective disorders. Six large meta-analyses of randomized, double-blind, placebo-controlled trials (each meta-analysis included between 19,000 and 87,000 patients) failed to show a significant difference in rates of suicides or suicide attempts with antidepressants compared with placebo [42–47]. The largest meta-analysis [47] even found significantly more suicides and suicide attempts (combined analysis) with SSRIs than with placebo. In addition, an analysis of long-term studies (8 weeks or longer) also did not find a difference between antidepressants and placebo [48]. A large retrospective cohort study (over 20,000 patients and over 60,000 patient-years at risk) of lithium and valproate given as prophylactic agents in bipolar disorder revealed a significantly lower rate of suicides and suicide attempts in patients treated with lithium [49].

7 Potential Mechanisms of Action of Lithium

Despite the established clinical efficacy, the specific mechanisms by which lithium exerts its effects on mood are not well understood [50–52]. At a morphologic level, lithium seems to preserve or increase the volume of brain structures involved in emotional regulation (prefrontal cortex, hippocampus, amygdala), possibly reflecting its neuroprotective effects. At a neuronal level, lithium reduces excitatory (dopamine and glutamate) but increases inhibitory (gamma-aminobutyric acid [GABA]) neurotransmission, although these general effects are accompanied by complex compensatory changes that strive to achieve homeostasis. At an intracellular and molecular level, lithium targets second-messengers, for instance phosphatidyl inositol (PI), cyclic adenosine-monophosphate (cAMP), and protein kinase C (PKC) pathways. As a putative consequence, lithium has been shown to reduce the oxidative stress that occurs with multiple affective episodes. It has been demonstrated that lithium increases protective proteins such as brain-derived neurotrophic factor (BDNF) and B-cell lymphoma 2, and reduces apoptotic processes through inhibition of glycogen synthase kinase 3 (GSK-3β).

Genome-wide association studies in bipolar disorders have been carried out. They suggest roles for the glutamatergic receptor AMPA (*GRIA2*) gene and the amiloride-sensitive cation channel 1 neuronal (*ACCN1*) gene in long-term lithium response, and a possible involvement of the sodium bicarbonate transporter (*SLC4A10*) gene in lithium response. Overall, it is clear that the processes that underpin the therapeutic actions of lithium are complex, most likely inter-related, and unique, making lithium different from all other psychotropic drugs [50–52].

8 Practical Issues of Lithium Therapy

Aiming at safe and effective lithium therapy, both the physician and the patient need to learn about and comply with different aspects of the treatment [53]. Lithium treatment is somewhat more complex than treatment with most other psychotropic drugs. However, it is not difficult to learn, and a good psychiatrist should know how to use lithium. If there is a clear indication for lithium, it should not be avoided because of irrational fear or ignorance.

8.1 Lithium Dose/Serum Level Monitoring

Regular monitoring of serum lithium levels is mandatory, because levels clearly above the therapeutic range are dangerous (see below). There is no standard lithium dose, but the patient's dosage must be determined individually based on their serum levels. The starting dose is typically between 450 and 600 mg lithium carbonate per day (some psychiatrists start with up to 900 mg/day) (450 mg lithium carbonate corresponds to 12.2 mmol of pure lithium). While lithium carbonate can be administered once daily, twice-daily administration every 12 h is more advisable to avoid lithium serum peaks. The serum lithium level should be checked for the first time after 3–7 days of daily intake. The therapeutic range is about 0.6–1.0 mmol/L. The blood needs to be drawn about 12 h after intake of the last lithium tablet.

For long-term treatment, the serum level should be at the lower end of the therapeutic range, and at the upper end for acute anti-manic treatment. However, in cases of insufficient efficacy, the approach of first choice is to increase the serum level within the therapeutic range. Conversely, in case of side effects, the serum lithium level should be lowered within the therapeutic range. With normal renal function, doubling of the daily dose will roughly result in a duplication of the serum level. Serum lithium levels should be monitored weekly until a stable individual dose is established. Intervals can then be prolonged. In long-term treatment, serum lithium levels should be checked at least

every 3 months. Kidney function (serum creatinine) and electrolytes (including calcium) should be checked at the same intervals, and thyroid-stimulating hormone (TSH) should be determined at least once a year. Hyponatremia leads to an increase in lithium level, which is why serum sodium should always be measured simultaneously with the lithium level.

8.2 Check-Up Before Lithium Treatment

Lithium is an element. Unlike other drugs, it cannot be metabolized by the body but is excreted unchanged by the kidneys. Hence, sufficient kidney function is necessary. Serum creatinine, as well as serum sodium, potassium, chloride, calcium, and TSH should be measured prior to treatment. In addition, a physical examination and a routine urine laboratory test should be completed. Females should not be pregnant. It is more precise to calculate the creatinine clearance by an equation such as the 'Modification of Diet in Renal Disease' (MDRD) formula, than to rely on serum creatinine alone.

The physician should repeatedly inform and advise the patient about the different aspects of lithium therapy (Table 1).

Contraindications are renal failure and acute myocardial infarction. Relative contraindications are renal insufficiency, psoriasis, Addison's disease, and pregnancy. Hypothyroidism is not a contraindication but should be treated with l-thyroxine.

8.3 Side Effects and Intoxication

Side effects (Table 2) can occur even within therapeutic lithium levels. A recent high-quality systematic review and meta-analysis [54] found a rather modest influence of lithium on renal function. The mean decrease in glomerular filtration rate was only 6.2 mL/min and not significantly different from that of controls. However, unfortunately, the review did not indicate the mean length of treatment under which this decrease was observed, or whether this decrease is progressive or stable over the time of lithium treatment. The mean maximum urinary concentration ability was significantly lower at 158 mOsm/kg, but this impairment is typically reversible after termination of lithium treatment. The rate of clinical hypothyroidism was significantly higher than in controls (OR 5.78, 95 % CI 2.00–16.67). Lithium can increase the parathyroid hormone (mean difference vs. controls 7.32 pg/mL [significant]) and, hence, increase serum calcium (difference vs. controls 0.09 mmol/L [significant]). Therefore, calcium should be monitored regularly. The review and meta-analysis confirmed a significantly greater weight gain compared with placebo. A clinically significant weight gain of >7 % was more frequent in patients receiving lithium than in patients receiving placebo (OR 1.89, 95 % CI 1.27–2.82, $p = 0.002$). However, weight gain with olanzapine was even greater (OR 0.32, 95 % CI 0.21–0.49, $p < 0{\cdot}0001$). No significant increase in congenital malformations, alopecia, or skin disorders was found [54].

In case of side effects, the first measure is to decrease the serum lithium level within the therapeutic range. If side effects persist, as with every drug, burden and gain of lithium treatment needs to be balanced together with the patient. Diarrhea can be avoided in most cases by switching to a lithium salt other than lithium carbonate (e.g., lithium sulfate or aspartate). In many countries, only lithium carbonate is available, and other lithium salts need to be obtained from international pharmacies. When switching to another lithium salt, it is essential that the mmol dose needs to be identical, not the mg dose. The different salts have different weights, but pharmacologically effective is only the molar lithium. However, in normal clinical

Table 1 Important points for physicians to impart to lithium-treated patients

Do not forget to drink
Do not go on a sodium chloride (table salt)-free or sodium chloride-reduced diet
If you are losing an extraordinary amount of water (e.g., sweating due to hot sun, sauna, hard physical work, or sport), drink additional water
If you have a fever, diarrhea, or vomiting, you will also lose water. Stop lithium intake and obtain serum lithium level control within the next 24 h if possible
You need to know the typical side effects of lithium (see Table 2)
You need to know the signs and symptoms of intoxication (see Table 3). If you suffer from one of these, stop lithium intake and obtain serum lithium level control as soon as possible. If it is serious, go to the hospital
Inform all your physicians that you are taking lithium
You (i.e., the patient) should know that drugs such as diuretics and other hypertension drugs, as well as non-steroidal anti-inflammatory drugs can increase the serum lithium level

Table 2 Side effects of lithium (can occur even when serum lithium levels are in therapeutic range)

Tremor (typically highly frequent and mild, predominately involving the hands; beta-blockers are helpful in some cases)
Diarrhea
Polyuria with consecutive polydypsia
Modest decrease in glomerular filtration rate and maximum urinary concentration ability
Weight gain
Hypothyroidism and goiter (note: hypothyroidism is not an indication to stop lithium, but to co-administer l-thyroxine; if l-thyroxine is given early enough, goiter will not develop)
First measure if side effects occur: try to lower the serum lithium level within the therapeutic range

Table 3 Signs and symptoms of lithium intoxication

Ataxia, dizziness
Low-frequency tremor
Dysarthria
Nausea and vomiting
Diarrhea
Rigor, hyper-reflexia, convulsions, somnolence, coma, death

routine, lithium carbonate is preferable due to an extended release effect.

Lithium intoxication exhibits typical signs and symptoms (Table 3). Serum lithium levels considerably above the therapeutic range can irreversibly damage the kidney and the cerebellum. Treatment in the intensive care unit is essential. Lithium intoxications above 2–3 mmol/L are life threatening.

8.4 Pharmacological Interactions

Diuretics, angiotensin-converting enzyme (ACE) inhibitors, and non-steroidal anti-inflammatory drugs lead to an increase in serum lithium levels. Consequently, the patient and all of his or her physicians should be informed about this. Where dosage changes in these drugs are necessary, corresponding controls of the serum lithium level and a re-evaluation of the lithium dose is required.

9 Conclusion and Recommendations

Lithium is the therapy of choice for long-term prophylactic treatment of bipolar disorder [9]. With regard to unipolar depression, lithium augmentation is an effective and evidence-based strategy for the everyday situation of a patient not responding to an antidepressant alone. It could even be argued that lithium augmentation is the first-choice option in these cases. In addition, lithium long-term prophylaxis is also an established strategy in unipolar depression, and an important alternative for non-responders to prophylactic treatment with an antidepressant. Last, but not least, the proven anti-suicidal properties make lithium a unique and life-saving substance.

However, one clearly has to recognize that lithium is considerably under-used, especially in Northern America. Several reasons may contribute to this discrepancy: lithium therapy is somewhat more complex than most other pharmacological treatments in psychiatry; lithium treatment outside the standards can be dangerous; lithium is cheap, and marketing strategies try to replace lithium with higher profit drugs. In this context, the risks and side effects of lithium have repeatedly been exaggerated in the past.

It is not difficult to learn how to use lithium. A safe lithium therapy for the benefit of the patient is possible. Older psychiatrists are called on to introduce younger colleagues to the use of lithium. Psychiatrists should be proud of their competence in lithium treatment. Antidepressants and second-generation antipsychotics can also be administered by general practitioners, but the use of lithium is an area of psychiatric expertise—as anticoagulation or insulin therapy is for internal medicine. The personal clinical experience of the author and many of his colleagues is that, of course, a considerable number of patients do not respond to lithium. However, those who do respond typically achieve full remission with a complete restoration of social functioning, which is rarely the case with antidepressants or antipsychotics. These patients are extremely thankful and do not wish to terminate lithium use for decades.

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